



Guideline topic: Pharmacological management of asthma
Evidence table 4.11d: Add-on drugs for inhaled steroids: Theophylline, beclomethasone dipropionate, budesonide

Author	Year	Study type	Quality rating	Population	Outcomes measured	Effect size	Confidence intervals / p values	Comments
Adults								
Evans ¹	1997	Crossover RCT	++	62 patients aged 18-97 (mean 38.8). Symptomatic despite 800-1000 µg inhaled corticosteroids. Mean FEV1 75% pred. (35-116%) 15% reversibility to b 2 agonists. Compared 800µg inh BUDE + low dose theoph OR 1600 µg inh BUDE. Study period of 3 months.	FVC FEV1 PEF Use of b 2 agonists	800µg BUDE plus theoph resulted in FVC and FEV1 <10% increase from baseline PEF increased in both groups ,25 l/min Reduced in both groups by ≈ 1 puff / 24 hrs	P=0.03 NS difference between treatments NS difference between treatments	In patients with persistent symptoms on up to 1mg/day inhaled budesonide, adding low dose oral theoph (serum conc <10mg/l) provided similar improvements in lung function, symptom control and b 2 agonist use to doubling the dose of inhaled corticosteroid to 1.6 mg/day.
Ukena ²	1997	RCT	+	133 patients	Increase in	≈ 20%	P<0.01 NS	In asthmatic

				aged 18-70 (mean 48.5) symptomatic despite 400mg BDP/day. FEV1 50-85% pred. 15% reversibility to β_2 agonists. Compared 400 μ g inh BDP + low dose theoph OR 800 μ g inh BDP. Study period of six weeks	home PEF Reduction in PEF variability Increase in FEV1 Symptom scores and use of β_2 agonist	am/pm PEF in both groups \approx 30% in both groups \approx 10% FEV1 in both treatments Improved significantly in both groups	difference between treatments. P<0.01 NS difference between treatments. P<0.01 NS difference between treatments. P<0.001 NS difference between treatments.	patients not controlled by 400 mg/day BDP, doubling the dose of BDP or adding theophylline provided equivalent improvements in asthma symptoms, lung function, and β_2 agonist use. Similar adverse events profile except that theoph. Associated more with mild GI symptoms.
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Children

Nassif ³	1981	Crossover + RCT		33 children aged 7-19. Comparison of theoph vs placebo in steroid dependent asthma with subgroups of 21 patients on 200-900 μ g / day inhaled BDP (mean 530 μ g / day) and 11 patients on alternate day prednisolone (mean dose 33	PEF Spirometry Asthma symptoms	PEF increased in inhaled BDP and oral prednisolone group. FEV1 increased in both groups. Patients were free of all symptoms 63%(+6,-6) of days compared	P0.02 before bronchodilator and p<0.05 after. P<0.01 P<0.01	In children with asthma on inhaled or oral corticosteroids, treatment with theophylline can improve the frequency and severity of asthma symptoms and improve lung function. Although there is evidence of reduced use of rescue steroid medication for exacerbations,
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				mg/day). Study period of 2 months.	Use of b 2 agonist	with 42%(+6,-6) on palacebo	P=0.02	no assessment of a true steroid sparing effect is made.
					Rescue with additional prednisolone	Inh b 2 agonist was required twice as often with placebo.		
						Additional daily corticosteroids were needed 3 times as often with placebo.		

1. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N Engl J Med 1997;337(20):1412-8.
2. Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, et al. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur Respir J 1997;10(12):2754-60.
3. Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. N Engl J Med 1981;304(2):71-5.